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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

OCTOBER 1944

RECENT EXPERIENCES WITH PENICILLIN IN THE TREATMENT OF SURGICAL INFECTIONS*

FRANK L. MELENEY

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THE Committee on Chemotherapy and Other Agents of the National Research Council has been given the authority by the War Production Board to direct the use of a certain part of the available penicillin for clinical investigation in civilian cases. During the past year the units studying the prevention of infection in accidental wounds and burns under the direction of the Subcommittee on Surgical Infections, have had the opportunity of using some of this penicillin in established surgical infections.

In the August 28, 1943, number of the *Jour. Amer. Med. Asso.*, Keefer and his associates on the Chemotherapy Committee[1] reported on the first 500 cases treated with penicillin. More recent reports have appeared covering smaller groups of cases by Dawson and Hobby,[2] Herrell,[3] and Bloomfield, Rantz, and Kirby,[4] but these papers did not distinguish medical from surgical infections. Lyons' excellent report of his experiences with returned wounded soldiers dealt with surgical

* Work done under contract with the Office of Scientific Research and Development. Presented with the consent of the Committee on Medical Research of the National Research Council at the Surgical Section of The New York Academy of Medicine April 7, 1944.

infections largely associated with compound fractures.[5] He brought out some important fundamental principles in this type of chronic surgical infection. But there has not been any presentation of various types of surgical infections treated with penicillin as far as we know. Inasmuch as the units studying purely surgical infections have now submitted records of over 275 cases and these have been observed from a surgical viewpoint and a tentative appraisal has been made of penicillin with consideration given to the natural course of surgical infections, it seems timely to present a review of these cases as a preliminary report. Summary sheets have been approved by the Subcommittee on Surgical Infections and Burns of the National Research Council for a more detailed study of established surgical infections and their treatment by sulfonamides, penicillin, and other antibacterial substances. A more definite appraisal of these agents will be possible when these records are available from a large number of cases. In this paper we would like to point out some of the differences between medical and surgical infections, to call attention to the difficulty of appraising drugs in surgical infections, and to present a few illustrative cases.

Surgical infections differ from medical infections in the following important respects. (1) There is a local breakdown of tissue or enclosed purulent exudation which either has to be evacuated or absorbed and which may nullify the effect of any antibacterial agent. (2) Thrombosed blood vessels in the walls of these areas of tissue breakdown may prevent the inflow of antibacterial agents from the blood stream into the area of bacterial activity. (3) Surgical infections are frequently due to a mixture of organisms, especially contaminated accidental wounds and war wounds and particularly gas gangrene. (4) Being local, surgical infections permit the local as well as the general administration of drugs. (5) Repair occurs with scar tissue and not a restoration of the tissues to normal as with medical infections. (6) The relation of the time of drug administration and the surgical procedure to the onset of the infection is extremely important in surgical infections. Presumably the drug acts best if given early during the stage of cellulitis before there has been much tissue breakdown. The surgical procedure may do the most good and the least harm if delayed. Both may be necessary to control the infection.

The history of man's fight against infection has been a series of exaggerated roseate hopes followed by disillusionment but progress has

been made—step by step. Ever since bacteria were found to be the cause of infections, panaceas have been sought for and frequently acclaimed, aided and abetted by the lay press with or without the encouragement of the discoverer or chief advocates. The goals of the doctors combating infections should be (1) the prevention of the entrance and the establishment of bacteria within the human body and (2) the destruction or the nullification of the action of any bacteria already established in the body.

There are so many factors operating in any case of surgical infection that it is difficult to evaluate the use of drugs. We must be cautious and not be carried away by too great enthusiasm but view the problem objectively. However, a drug may be said to be effective in surgical infections if it (1) obviates surgery in a condition otherwise requiring incision, (2) permits a more limited surgical procedure than usual, (3) shortens the time of control of the infection, (4) permits primary closure after incision or (5) permits earlier secondary closure than usual.

The discoverers and proponents of penicillin have been conservative in their claims and have tried hard to evaluate it and find the best way to administer it. Fleming,[6, 7, 8] Florey,[9, 10] Chain[11] and Garrod[12] deserve great credit for their painstaking conservatism in the development of the drug and the critical, scientific, logical methods that they have used to demonstrate its indications and its limitations. In this country its potential value to the war effort has led the War Production Board to maintain complete control of the supply and limit its use to the Army, the Navy, and accredited individuals under the Committee on Chemotherapy and Other Agents. From these cases of surgical infections treated by the surgical units the following data have been submitted—the diagnosis, the bacteriology, the method, amount and duration of drug therapy, the time relationship of drug treatment to the onset of infection and to the surgical procedure, if any. The results have been recorded as (1) excellent or brilliant with an almost immediate response (within 48 hours), (2) good—slower but definite benefit, (3) questionable, when the case might have done as well without the drug, and (4) no effect when the infection went its usual course.

Until more cases have become available and more details can be analyzed only the most obvious trends can be seen. Fully developed conclusions cannot be drawn.

PENICILLIN TABLE I—MARCH 1, 1944
ESTABLISHED SURGICAL INFECTIONS

Method Used	*Total*	*Results*			
		Excellent	*Good*	*Questionable*	*No Effect*
General only	144	55(38.2%)	40(27.8%)	22(15.3%)	27(18.7%)
Local only	64	13(20.3%)	23(36.0%)	17(26.6%)	11(17.2%)
Both local and general	67	22(32.9%)	20(29.9%)	12(17.9%)	13(19.4%)
TOTAL	275	90(32.7%)	83(30.2%)	51(18.5%)	51(18.5%)
Surgery	155	48(31.0%)	51(32.9%)	31(20.0%)	25(16.1%)
No surgery	120	42(35.0%)	32(26.6%)	20(16.7%)	26(21.7%)

In surgical infections the opportunity is given for three methods of drug therapy, general, local, and combined. In Table I the 275 cases are divided into these three groups and the results recorded for each. For the most part the cases receiving general treatment gave some clinical evidence of systemic spread either of the bacteria themselves or their poisons. For that reason they were generally more serious than those receiving local treatment only. Those treated locally offered the opportunity for local application of the drug, in most instances after a surgical incision but at times following simple aspiration of a purulent collection. It is of interest that the sum total of favorable results are remarkably even in the three groups but the highest percentage of brilliant results occurred in those receiving general treatment only and the "excellent" outweighed the "good." While in the cases with only local treatment, the "good" outweighed the "excellent." This may be explained by the fact that in the "general" group there were many early cases in which the infection was in a stage of cellulitis while in the local group there had been a breakdown of tissue which took time to be evacuated or absorbed even after surgical incision. It is obvious that this table needs a careful breakdown and analysis before methods of administration can be compared one with another. Conclusions cannot be drawn from it.

Table I also reveals that 120 of these 275 cases, ordinarily classed as surgical infections, did not have a surgical incision. Aspiration was

PENICILLIN TABLE II

MARCH 1, 1944

Diagnoses	*Totals*	*Results*			
		Excellent	*Good*	*Questionable*	*No Effect*
Staphylococcus aureus septicemia, cryptogenic	6	3	1	1	1
With endocarditis	6	..	..	..	6
With endocarditis (?)	1	1	..	..	..
With acute osteomyelitis	15	8	6	1	..
With suppurative arthritis	2	2	..	..	..
With meningitis	1	..	..	..	1
With brain abscess	1	1	..	..	..
With multiple abscesses	1	..	1	..	..
With third degree burn	2	1	..	..	1
With pemphigus	1	..	..	..	1
With diabetes	2	..	1	..	1
With furunculosis	3	..	3	..	..
With cellulitis of face	2	2	..	..	..
With cavernous thrombosis (?)	1	1	..	..	..
With cellulitis of chest wall	1	1	..	..	..
With lung abscess	2	1	..	..	1
With empyema	1	1	..	..	..
With patent ductus	1	1	..	..	..
With pyonephritis	2	2	..	..	..
Following hysterectomy	1	..	1	..	..
TOTALS	52	25(48%)	13(25%)	2(4%)	12(23%)
Hemolytic streptococcus septicemia	8	2	2	..	4
Non-hemolytic streptococcus septicemia	1	1	..	..	..
Anaerobic streptococcus septicemia	3	1	..	1	1
Staphylococcus albus septicemia	1	1	..	..	..
TOTALS	13	5	2	1	5

PENICILLIN TABLE III—MARCH 1, 1944

Other Main Diagnoses (I)	*Total*	*Results*			
		Excellent	*Good*	*Question-able*	*No Effect*
Chronic osteomyelitis	39	6	15	10	8
Acute osteomyelitis	4	3	1	..	..
Suppurative arthritis	10	3	3	3	1
Suppurative arthritis with osteo	3	2	1	..	..
Compound fracture	14	5	7	1	1
Infected operative wound	8	1	3	3	1
Infected burn	9	2	2	2	3
Superficial abscess	27	10	10	3	4
Deep abscess	5	1	2	2	..
Gas gangrene (Welchii)	5	2	..	3	..
Gas gangrene (Novyi)	1	1	..	..	..
Gas gangrene (Serdellii)	1	..	..	..	1
Empyema	9	1	..	4	4
Lung abscess	2	..	1	1	..
Post-operative pneumonitis	1	..	1	..	..
TOTAL	138	37	46	32	23

done in many of these cases but no cutting. And yet the results in the four classifications are almost as good as in the cases which were operated upon. A detailed analysis however would show that these two groups are not comparable. The cases operated upon had the largest number of serious cases and in many of them treatment was instituted late while in the non-operated group treatment was frequently instituted early—in the stage of cellulitis before there was any indication for surgery. However in many of these cases drug treatment obviated what would otherwise have been necessary surgery.

Table II shows the cases of septicemia. Fifty-two of these were due to the hemolytic Staphylococcus aureus and the results indicate a favorable response in 73 per cent of cases. Of the twelve cases in which there was no effect six were demonstrated to have endocarditis and the other six may have had foci hardly approachable either by the drug

PENICILLIN TABLE IV—MARCH 1, 1944

Other Main Diagnoses (II)	*Total*	*Results*			
		Excellent	*Good*	*Question-able*	*No Effect*
Actinomycosis	6	1	4	1	..
Ulcer of skin	9	4	2	1	2
Chronic undermining ulcer	2	..	..	1	1
Cellulitis of face	3	2	1	..	..
Cellulitis of neck	6	2	2	2	..
Cellulitis of orbit	4	3	1	..	..
Carbuncle	6	3	2	1	..
Furunculosis	3	..	3	..	..
Pemphigus	1	..	..	..	1
Pyoderma	2	..	..	2	..
Erysipeloid	2	2	..	..	..
Peritonitis	3	..	2	..	1
Subphrenic abscess	4	..	..	2	2
Liver abscess	3	2	..	1	..
Pelvic thrombophlebitis	2	2	..	..	..
TOTAL	56	21	17	11	7

or by a surgical procedure. That almost half of these septicemias had a brilliant result and another quarter a frankly good result, strongly suggests that penicillin is meeting a real therapeutic need in a disease formerly producing a mortality of 80 per cent and which was not met by the sulfonamides. The results were not so good in the small series of hemolytic streptococcus septicemias where the table indicates a favorable outcome in only 50 per cent. However it should be noted that the smallness of this series is itself a triumph for the sulfonamides which have made hemolytic streptococcus septicemia a rare disease. This table obviously needs more detailed analysis.

Table III gives clinical diagnoses which permit certain groupings with their results. It is seen that the response in the cases of chronic osteomyelitis leave something to be desired. This group needs a more detailed analysis to bring out the reasons for success on the one hand

PENICILLIN TABLE V—MARCH 1, 1944

Miscellaneous Diagnoses	*Total*	*Results*			
		Excellent	*Good*	*Question-able*	*No Effect*
Brain abscess with osteo. skull	1	..	1	..	..
Meningitis, cav. sinusitis with osteo skull	1	..	1	..	..
Meningitis from abscess face	1	..	..	..	1
Mastoiditis	2	1	1	..	..
Bronchiectasis	1	1	..	..	..
Gangrene of foot	3	1	..	2	..
Osteochondritis	1	..	1	..	..
Infected skin graft	1	1	..	..	..
Human bite	2	..	1	..	1
Ulcerative colitis	1	..	..	..	1
T. B. sinus with secondary infection	2	..	..	1	1
TOTAL	16				

and failure on the other, the factors of duration of illness, extent of disease, necrosis of tissue, and nutritional depletion being of particular importance. The results are more favorable in acute osteomyelitis, suppurative arthritis, compound fractures, and in superficial abscesses.

The small group of gas gangrene cases requires careful study. The details have not been furnished in all of these cases, but certain things stand out. It must be constantly borne in mind that gas gangrene is almost always a polymicrobic disease with necrosis of tissue. One of the seven cases was due predominantly to C. oedematiens. The result was said to be excellent but amputation was deemed necessary. This was done through and not above the involved tissue. One was due primarily to C. sordellii. Although welchii was also present, there was no gas or necrosis of tissue—but a malignant edema; 50,000 units of penicillin every three hours had no efiect, obviously not enough. In two of the Welch cases the result was called excellent but amputation was required. This classification seems faulty here because amputation can hardly be considered the result desired. In the three questionable cases the value of penicillin could not be determined with certainty. In one

PENICILLIN TABLE VI—MARCH 1, 1944

Bacteria	*Totals*	*Results*			
		Excellent	*Good*	*Question-able*	*No Effect*
Staphylococcus aureus	121	47	44	15	15
Hemolytic streptococcus	13	4	4	..	5
Both S. A. and H. S.	11	3	4	3	1
Other mixtures	85	19	18	24	24
Anaerobic strept.	3	1	..	1	1
Staphylococcus albus	4	1	..	3	..
Coagulase micrococci	4	1	2	..	1
C. welchii (perfringens)	2	1	..	1	..
C. welchii sordellii	1	..	..	..	1
C. novyi (edemetiens)	1	1	..	..	..
C. welchii and Hem. strept.	1	1	..	..	..
Non hemolytic strept.	1	1	..	..	..
E. coli	2	..	1	..	1
Pneumococcus	3	2	1	..	..
Actinomycosis	5	..	4	1	..
Erysipeloid (clinical)	2	2	..	..	..
Non-hemolytic staphylococcus	1	1	..	..	..
Unknown	15	5	5	3	2
TOTAL	275	90	83	51	51

of these amputation was done. The favorable results in gas gangrene cases with penicillin reported from the combat zones have also for the most part been in cases where amputation was done. The accredited effect was obtained by continued use of the drug after amputation. It has been reported that penicillin permitted amputation through the diseased tissue, leaving some in, whereas without the drug, amputation to be successful had to be above the site of the disease. This would not seem to be a very clear cut demonstration of the value of the drug, leaving much to be desired. It would seem to be essential to explore other methods of combating this infection, and perhaps methods should be vigorously pursued of combating the associated organisms, particu-

PENICILLIN TABLE VII—MARCH 1, 1944

DOSAGE—GENERAL

Including those cases with general and with combined general and local treatment

Units	*Totals*	*Results*			
		Excellent	*Good*	*Question-able*	*No Effect*
Up to 250,000	37	8	7	7	15
Over 250,000 up to 500,000	53	27	10	8	8
Over 500,000 up to 750,000	29	6	15	3	5
Over 750,000 up to 1 million	24	9	7	7	1
Over 1 million	62	25	19	9	9
Not stated	6	2	2	0	2
TOTALS	211	77	60	34	40

DOSAGE—LOCAL

Including those cases with local and with combined general and local treatment

Units	*Totals*	*Results*			
		Excellent	*Good*	*Question-able*	*No Effect*
Up to 10,000	46	13	17	9	7
Over 10,000 up to 20,000	10	2	3	2	3
Over 20,000 up to 30,000	5	1	1	3	..
Over 30,000 up to 40,000	4	1	1	1	1
Over 40,000 up to 50,000	5	2	1	2	..
Over 50,000	39	7	11	11	10
Not stated	22	9	9	1	3
TOTALS	131	35	43	29	24

larly the Gram-negative bacilli so often present, which frequently inactivate the penicillin.

Table IV lists smaller groups which are hardly susceptible of analysis but the general trend is favorable particularly in those cases which were superficial and approachable by local treatment or were in the stage of cellulitis when treatment began.

Table V lists miscellaneous cases of relatively minor importance.

Table VI indicates the bacteriology and three points seem to stand out. The first of these is the importance of knowing with certainty the bacterial etiology of all of these infections, for it is obvious that prognosis depends upon this knowledge. It is clear that highly favorable results may be expected in 75 per cent of the pure hemolytic Staphylococcus aureus cases but the response is less favorable in the hemolytic streptococcus infections and where there are mixtures of organisms. These cases must be further analyzed with respect to preceding treatment. Just which mixtures responded and which resisted may well bring out some interesting ideas regarding bacterial synergism and antagonism. While the cases of actinomycosis showed some initial success, time must be given for a final appraisal of this type of infection.

Dosage is shown in Table VII and it is at once apparent that less than a quarter of a million units systemically is frequently ineffective. It must be remembered however that in this group are those fulminating cases which died before adequate dosage could be given as well as those receiving inadequate dosage over a longer period of time. The results in the other groups show very similar percentages on the favorable side, namely 71 per cent, 72 per cent, 66 per cent, 71 per cent. However the dosage for general administration and the consideration of the intravenous versus the intramuscular route need detailed analysis. Lyons[5] has emphasized the need for larger doses in staphylococcal than in other types of infection, but in this series the pure staphylococcal group has done particularly well on relatively small doses—frequently 40,000 units have given brilliant results in serious cases. Of course, 80,000 units might have given a more comfortable margin and accomplished the results more quickly. It must be remembered that Lyons' cases were for the most part compound fractures where necrotic tissue and associated proteolytic organisms and lowered nutritional status were factors of major importance. It would seem reasonable in pure staphylococcal infections to start off with 80,000 to 100,000 units and in mixed infections to double this amount. Then, if the result is not satisfactory in 24 or 48 hours, these doses may be increased.

Local dosage of less than 10,000 units has been frequently favorable in well localized infection. It is obvious however that much more study must be given to the concentration, dosage, frequency of administration and the vehicle to be used for local administration.

Table VIII reveals that in the great majority of these cases sulfona-

PENICILLIN TABLE VIII—MARCH 1, 1944

PREVIOUS SULFONAMIDE TREATMENT

	Totals	Results			
		Excellent	Good	Questionable	No Effect
No previous treatment of any kind	45	14	14	12	5
Sulfadiazine	171	58	53	25	35
Sulfathiazole	35	9	11	9	6
Sulfanilamide	11	6	4	1	..
Sulfamerizine	2	1	..	1	..

ACCOMPANYING SULFONAMIDE TREATMENT

	Totals	Results			
		Excellent	Good	Questionable	No Effect
No accompanying drug treatment	172	57	47	40	28
Sulfadiazine	34	10	5	4	15
Sulfathiazole	2	..	1	..	1
Sulfanilamide	2	1	1	..	..
Sulfapyridine	1	..	1	..	..
Sulfamerizine	1	..	1	..	..
Sulfacetamide	1	..	..	..	1

DURATION OF TREATMENT

	Totals	Results			
		Excellent	Good	Questionable	No Effect
Up to 5 days	41	10	8	12	11
6 to 10 days	62	19	25	9	9
11 to 15 days	47	16	12	10	9
16 to 20 days	28	8	11	4	5
Over 20 days	31	9	10	10	2
Not stated	66	28	17	6	12
TOTALS	275	90	83	51	51

mides have been used previously without effect and the results have been just about as good in these cases as in those not previously treated by anything. In a certain number of cases, sulfonamides have been used along with the penicillin or subsequently if penicillin alone failed to control the infection. This synergism of the two drugs needs further study.

With regard to the duration of the treatment it would appear that a minimum of six days is advisable. In the shorter group are not only the fulminating cases but those in which treatment was terminated promptly following a prompt resolution of the process. It is obvious however in several of these cases that a wider margin of safety would have been preferable.

An analysis of the causes of failure or questionable results reveals two outstanding associated conditions, namely the presence of necrotic tissue and/or a mixture of organisms. A few cases were fulminating or the patients were moribund and treatment was obviously instituted too late. Occasionally organisms belonging to susceptible groups were found to be resistant to penicillin, but for the most part the failures were in cases of polymicrobic infections which included Gram-negative bacilli. Where hemolytic staphylococci and hemolytic streptococci were present together, the infection was often much more virulent than in pure infections with either of these organisms. Larger initial doses may be indicated in such cases. There are among these failures and questionable results many cases in which the cause of failure is not apparent—cases in which the organisms were susceptible and yet nothing happened. It will require a more careful study of the details of these cases before the cause for failure can be determined.

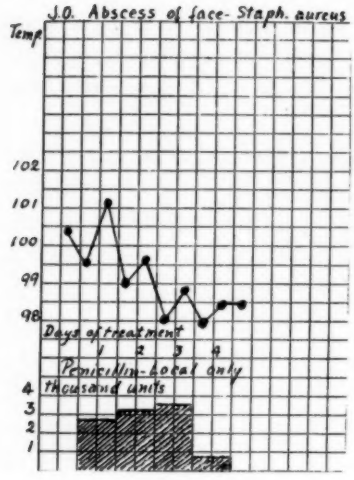
Certain of the individual cases bring out some interesting points and are therefore briefly abstracted. The temperature curves and dosage graphs are shown in the accompanying figures, page 530.

Summary

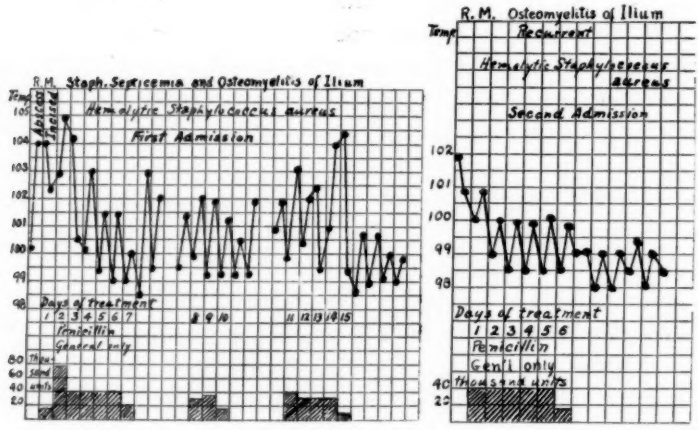
1. A preliminary analysis has been made of 275 cases of surgical infections treated with penicillin by a group of surgeons* directing the

* Case records included in this summary have very kindly been sent in by Drs. Max Zinninger and William Altemeier of Cincinnati, John Lockwood and William White of Philadelphia, Warfield Firor and Eleanor Bliss of Baltimore, Alton Ochsner, Guy Caldwell, and Maxwell Kepl of New Orleans, Roy McClure, Conrad Lam and John Hirshfeld of Detroit. The abstracts and temperature curves are from cases from the Presbyterian Hospital in New York under the supervision of Harold Harvey, George Humphreys, Robert Elliott and Frank Meleney. Acknowledgement is gratefully made herewith.

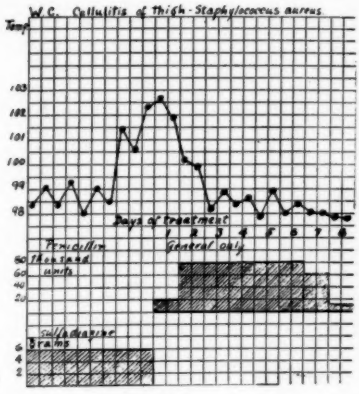
(CONTINUED ON PAGE 537)



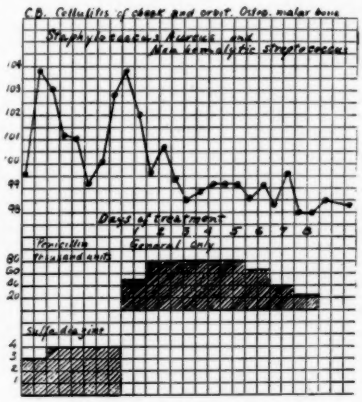
Case I: J. O. A girl of 17 with a history of two facial abscesses, incised and slow to heal, had a third and larger hemolytic Staphylococcus aureus abscess of the cheek, with swelling in the floor of the mouth. Local instillation only, of about 3000 units of penicillin once daily for three days resulted in prompt resolution of the process.



Case II: R. M. A boy of 15 with a hemolytic Staphylococcus aureus septicemia following a boil on the knee, a bruise of the hip, and an evening toss in a lake, failed to respond to sulfonamides or incision of an abscess over the ilium. The septicemia cleared with 40,000 units of intramuscular penicillin daily although metastases threatened to develop in the lungs. While the wounds healed, progressive destruction of the ilium occurred, and during convalescence an abscess developed on the inner surface of that bone. This however resolved without incision following a second short series of penicillin treatments. Thereafter symptoms completely subsided and have not recurred in over a year. Furthermore X-ray films reveal a regeneration of the bone.



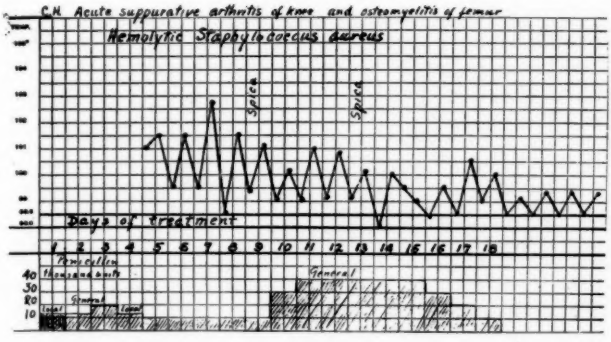
Case III


C.B. Cellulitis of cheek and orbit. Osteo. malar bone
Staphylococcus Aureus and Non hemolytic streptococcus
Days of treatment
1 2 3 4 5 6 7 8
Penicillin thousand units
General only
Sulfadiazine

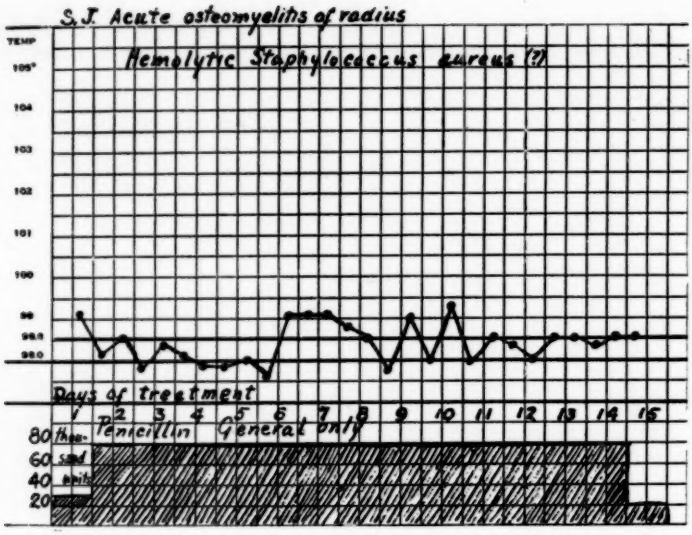
Case IV

Case III: W. C. A boy of 16 had an acute hemolytic Staphylococcus aureus diffuse cellulitis of the thigh threatening septicemia and suppurative arthritis of the knee. Failing to respond to sulfadiazine, it resolved promptly following systemic intramuscular administration of 80,000 units of penicillin daily for a week.

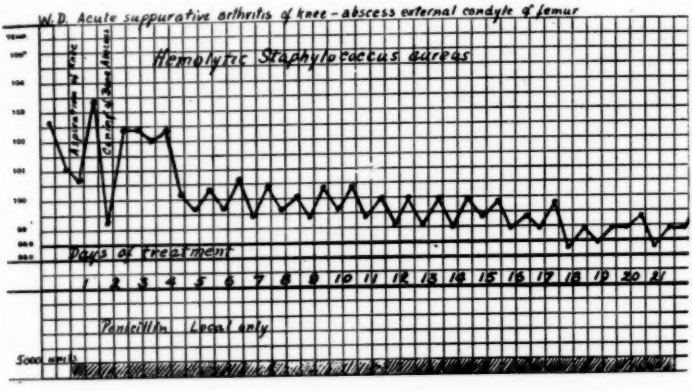
Case IV: C. B. A doctor of 32 had a hemolytic Staphylococcus aureus and nonhemolytic streptococcus cellulitis of the cheek and orbit following a Caldwell-Luc operation of the antrum. It failed to respond to the sulfonamides, although the temperature fell initially it sharply rose again. After the second dose of 10,000 units of intramuscular penicillin the patient volunteered the information that he suddenly felt free of the infection. The local process rapidly subsided but X-rays revealed some osteomyelitic changes of the malar bone which may be heard from later.


C.H. Acute suppurative arthritis of knee and osteomyelitis of femur
Hemolytic Staphylococcus aureus
Spica
Spica
Days of treatment
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Penicillin thousand units
General

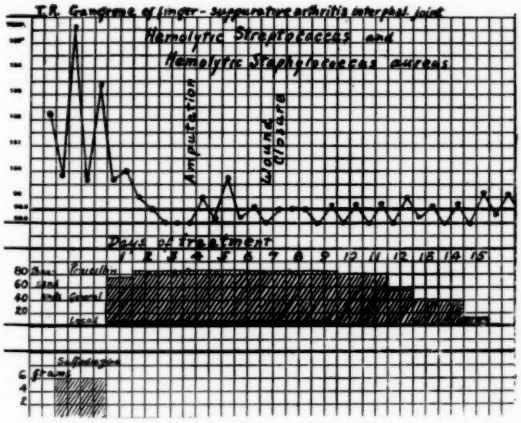
Case V: C. H. A boy of 11 came in suffering from a hemolytic Staphylococcus aureus osteomyelitis of the femur and suppurative arthritis of the knee. Before admission he was given relatively small doses of penicillin intramuscularly and locally by needle into the knee joint. The process subsided following repeated aspiration of the knee joint and immobilization in a spica without further operative procedures.



Case VI: S. J. A boy of 18 who had had an old history of recurrent osteomyelitis of the tibia, developed a sudden acute osteomyelitis of the radius. Five of seven attending surgeons judged that it would need surgical drainage. He was given intramuscular penicillin 10,000 units every three hours for fourteen days. The process promptly began to resolve and in three weeks he was able to return to work. X-ray films showed a progressive regeneration of the bone.

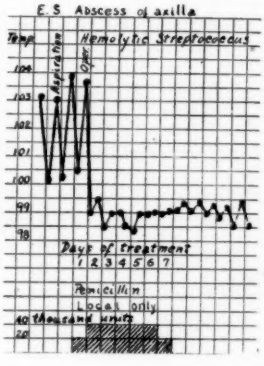

W.D. Acute suppurative arthritis of knee - abscess external condyle of femur
Hemolytic Staphylococcus aureus
Aspiration of Knee
Curetted of Bone Abscess
Days of treatment
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
Penicillin Local only
5000 units

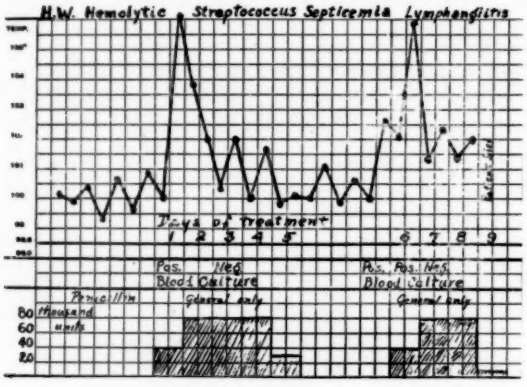
Case VII: W. D. A boy of 14 had had a sequestrum removed from a sinus tract leading down from a suppurative focus in the external condyle of the femur five years previously. He returned with a large bone abscess filling the external condyle and a suppurative arthritis of the knee joint. The knee was aspirated and 5000 units of penicillin were instilled just once. Next day the bone abscess was coned out and packed with gauze soaked in 5000 units of penicillin within a China silk tampon. The penicillin soaked packing was changed daily thereafter and the silk tampon was removed on the seventh day when the bone cavity was found to be lined with granulations. They quickly filled up the cavity and the patient left the hospital on the 27th day. The wound was fully healed in seven weeks. The knee joint returned to perfect function without incision or further aspiration.



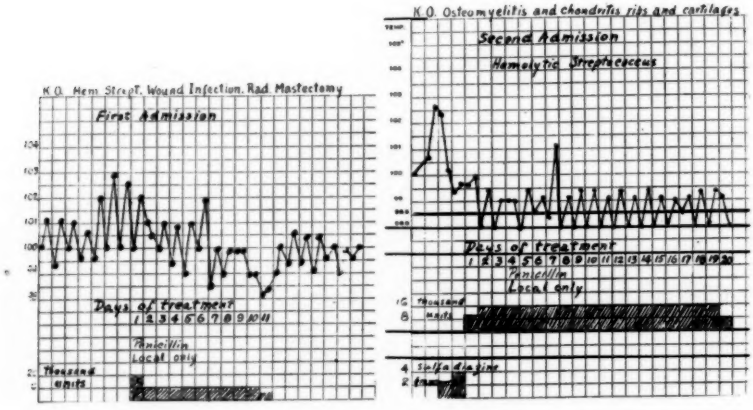
Case VIII: T. R. A Merchant Marine cadet of 20, six weeks before admission had injured his left index finger while cleaning an engine head. It became infected and a slow gangrenous process developed alongside the nail. Two weeks before admission a similar area of gangrene developed over the proximal interphalangeal joint. This slowly ate down to the extensor tendon, dissolved it and consumed the cartilage of the joint. Cellulitis then spread alarmingly up the hand. Both hemolytic streptococcus and hemolytic Staphylococcus aureus were cultured from the wound obviously acting in synergism to produce a gangrenous type of infection. No anaerobes were found. The process was checked by local and intramuscular penicillin. Three days later the finger was amputated at the joint with a long anterior skin flap which was closed on the third day when cultures revealed a disappearance of the streptococcus and marked decrease of the staphylococcus. The wound healed by primary union.

Case IX: E. S. A woman of 62 developed a huge abscess of the axilla following a hemolytic streptococcus infection of the hand; 400 cc of pus were removed by aspiration and 1000 cc more next day through a small incision. Tubes were inserted into the cavity through which 10,000 units of penicillin were introduced every six hours for six days. The fall in temperature was abrupt and convalescence was rapid. Perfect function of the arm resulted.

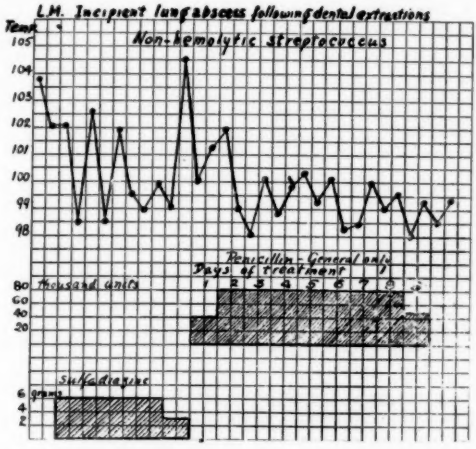




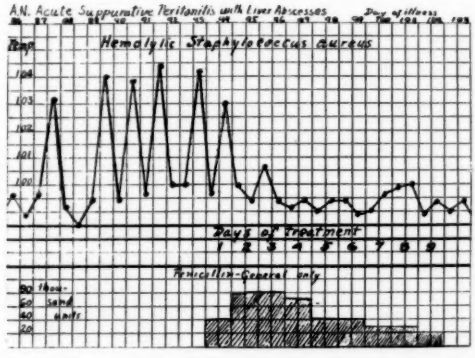
Case X: H. W. A man of 63 with a history of six previous coronary attacks developed a hemolytic streptococcus septicemia following a cellulitis of the thumb. Lymphangitis of the arm followed incision of the thumb and the temperature rose to 106. Temperature fell promptly following the intramuscular administration of 10,000 units of penicillin every three hours and the blood culture became sterile. Penicillin was stopped after four days but three days later the septicemia recurred with another spike of temperature to 105 without obvious reactivity at the portal of entry. Penicillin was resumed and the temperature again fell and blood culture again became sterile. Fluid collected in both chests and was removed by tapping. Cultures yielded no growth. However venous pressure gradually mounted to over 200 and he suddenly died on the fourth day of the second series of penicillin treatments.


K.O. Hem. Strept. Wound Infection. Rad. Mastectomy
First Admission
Days of treatment
1 2 3 4 5 6 7 8 9 10 11
Penicillin
Local only
Thousand units
K.O. Osteomyelitis and chondritis ribs and cartilages
Second Admission
Hemolytic Streptococcus
Days of treatment
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Penicillin
Local only
Thousand units
Sulfadiazine

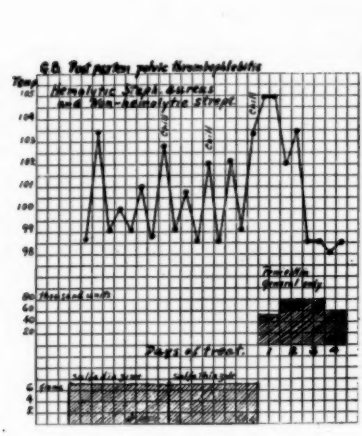
Case XI: K. O. A woman of 52 developed a wound infection yielding hemolytic streptococci following a radical mastectomy. Local penicillin 10,000 units daily was of questionable benefit but the infection slowly cleared up. Within a few weeks however infection recurred in the ribs and cartilages. After surgical removal of the diseased bone and cartilage and continued local treatment with 16,000 units of penicillin daily, the wound finally closed and has remained closed for four months.



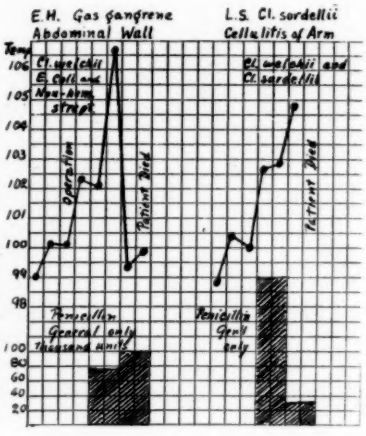
Case XII: L. M. A hospital supervisor of 53 developed signs of pneumonia and incipient lung abscess, six days after the extraction of seven infected teeth. She failed to respond to sulfadiazine and the disease continued to spread in the lungs. Following the intramuscular injection of 10,000 units of penicillin every three hours the process steadily but slowly resolved. She complained bitterly of pain at the site of injection but accepted it for a full course of eight days.



Case XIII: A. N. A man of 64 had been ill with recurrent chills and fever and jaundice for two months. A sudden development of severe upper abdominal pain led to an exploration. Pus was extensively spread around the upper abdomen and masses were found in the liver presumably liver abscesses. The abdomen was closed without drainage. Unfortunately the cultures of the pus yielded no growth. After operation two blood cultures were negative but the fifth postoperative day following a chill, a blood culture yielded hemolytic Staphylococcus aureus in one flask. He was given sulfadiazine but he ran an irregular fever for 24 days. Then he began to spike daily up to 103-104 with frequent chills. Intramuscular penicillin was started on the 31st postoperative day and continued with 10,000 units every three hours. Temperature fell dramatically and remained normal thereafter and penicillin was continued for nine days. He left the hospital four days later.


G.B. Post partum pelvic thrombophlebitis
Hemolytic Staph. aureus and Non-hemolytic strept.
Penicillin Gram only
Days of treat.
1 2 3 4

Case XIV



Case XV and XVI

Case XIV: G. B. A woman of 27 developed a postpartum pelvic thrombophlebitis beginning on the third day with daily spikes of temperature and frequent chills. Cultures of the lochia revealed hemolytic Staphylococcus aureus and non-hemolytic streptococcus. Temperature fell dramatically on the second day of intramuscular penicillin with 10,000 units every three hours and remained normal. Penicillin was continued for only two more days and her symptoms did not recur. This was probably an unsafe margin but enough in this instance.

Case [illegible] A woman of 51 developed a gas gangrene of the abdominal wall following [illegible] of a common bile duct from which stones were removed and a culture obtained [illegible] Cl. welchii, E. coli and non-hemolytic streptococcus. The rectus muscle above the oblique R. U. Q. wound was found liquified and was scraped out. Zinc peroxide was applied locally and both penicillin and polyvalent gas gangrene serum were given intravenously—the penicillin was given in doses of 50,000 units every three hours. During the night, the tempertaure rose to 106° and then fell in the morning to 99°. She seemed better but jaundice supervened with signs of pulmonary edema and she suddenly died. The benefit of penicillin was questionable. Autopsy showed no evidence of gas in the tissues and the local process seemed to be controlled. She evidently died of the pulmonary and hepatic toxemia.

Case XVI: L. S. A woman of 31 came to the hospital with a rapidly spreading edema of the left arm following a hypodermic injection for asthma. It was at first thought to be an allergic reaction. She repeatedly went into shock only to be restored temporarily by plasma. Incision revealed an edematous fluid which cultured Cl. sordellii in large numbers and Cl. welchii in decidedly smaller numbers. There was no gas in the tissues nor involvement of the muscle. She was given 50,000 units of penicillin intravenously every three hours but this was obviously ineffective for the edema spread relentlessly. Further incisions likewise failed to halt the spread of the process down the forearm to the hand and over onto the chest wall. Temperature rose steadily to 104° and she died on the 5th day 22 hours after the administration of penicillin during which she received 230,000 units.

study of established infections under the Subcommittee on Infected Wounds and Burns of the National Research Council.

2. A more detailed analysis from a surgical viewpoint of these and other similar cases will have to await the availability of special summary sheets which have been approved by the Subcommittee on Infected Wounds and Burns and by Chairman Lowell Reed of the Subcommittee on Biostatistics of the National Research Council.

3. The differences between medical and surgical infections have been pointed out and the difficulty of evaluating drugs in the treatment of surgical infections has been reiterated.

4. Certain criteria for demonstrating the value of drugs in surgical infections have been proposed.

5. Tables have been presented grouping the cases according to diagnosis, bacteriology, method and dosage and duration of penicillin administration and associated surgical procedures as well as previous and accompanying sulfonamide treatment. The results have been listed as "excellent," "good," "questionable," and "none."

6. Brief clinical abstracts and figures have been presented of illustrative cases with graphs showing the relationship of temperature curves to drug treatment.

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PHYSIOLOGICALLY DIRECTED THERAPY IN THE TREATMENT OF INTRACTABLE BRONCHIAL ASTHMA*

ALVAN L. BARACH

INTRODUCTION

THE purpose of this paper is to present a method of treatment that is derived neither from the allergic nor the simply palliative approach but more especially from an evaluation of the disturbed physiology that results from persistent bronchial spasm. Although a cure of the disease is not the aim of physiologically directed therapy, a more lasting freedom from the symptoms of severe asthma takes place with sufficient frequency as to justify a review of the principles on which it is based. It should be emphasized at the outset that every patient with bronchial asthma should be investigated carefully by a physician with special training in allergy, and that the present program for the relief of intractable asthma is not intended as a substitute for the search for specific etiological factors.

A frequent observation of doctors who see patients with bronchial asthma is that a remission in the disease at times takes place in which the patient is for a variable period free from the distressing symptoms of more or less continuous asthma. This abrupt cessation of bronchial spasm has been seen after an acute illness with high fever, such as pneumonia. The intention of physiologically directed therapy is to initiate a somewhat similar remission and to provide the means of maintaining it for a relatively prolonged period. The principle of treatment consists of repeated bronchial relaxation by the cumulative effect of various measures which act in this direction. Although remissions in intractable asthma were first obtained by the author as a result of intermittent inhalations of helium-oxygen mixtures, repeated bronchial relaxation may now be secured in many cases without the use of helium therapy.[1,2,3,4] In cases in which the provision of effective helium therapy

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is not feasible, the continuous administration of oxygen is indicated if anoxia is present, to overcome the effects of oxygen want on the cardio-respiratory and central nervous systems. The disadvantage of prescribing helium is the technical difficulty of administering it efficiently, as well as the expense of the gas itself and frequently an incomplete understanding of the purpose for which it is intended. For these reasons other measures, including the effective use of aminophyllin, may well be tried first.

Pathological Physiology of Obstructive Dyspnea

The consequences of experimental tracheal constriction in dogs will be briefly reviewed since the effects produced in this way may aid our understanding of obstructive dyspnea in man. When a dog is required to breathe through a constricted orifice, such as one-eighth of an inch, the increased physical effort made necessary is immediately portrayed by a marked rise in negative intrapleural pressure during the inspiration and by a pressure during expiration which approaches that of the atmosphere. Prolonged obstructive dyspnea results in congestion and edema of the lungs, more marked at the bases, with areas of emphysema at the periphery. If an animal is subjected to tracheal constriction only during the *inspiratory* cycle, with expiration free, these changes are still present, since the elevated negative pressure within the chest results in a suction action on the alveoli and on the intrathoracic bronchi, with the production of edema in the alveoli and swelling of the bronchial mucous membranes.[5,6,7] In addition, there is a readier inflow of blood into the lungs and an increased difficulty in the exit of blood from the lungs into the left heart and from the left heart into the aorta. The pulse becomes more rapid, the volume disappears during the inspiratory cycle and the dog finally dies of asphyxia, due to extensive damage in the lungs and cardiac failure.

When inspiration is allowed to be free and tracheal constriction is created during expiration, the changes just described do not take place and the animal at the end of six hours appears to be in good condition. The conclusion to be drawn from separating the effects of obstruction during inspiration from those during expiration is that the heightened negative pressure within the lung during the inspiratory cycle is the critical pathogenetic factor responsible for damage to the lungs.

When obstructive dyspnea is due to constriction in the larynx or

in the trachea outside the chest, inspiration and expiration are equally prolonged. The increase in the volume of breathing is at first stimulated by proprioceptive reflexes from the lungs. Later, as pulmonary congestion and edema take place, as well as swelling of the mucous membrane of the bronchi, dyspnea is aggravated by anoxia and accumulation of carbon dioxide. The increased ventilation may in the beginning result in a blowing off of carbon dioxide, with a transient and slight shift in pH toward the alkaline side but as pathological changes take place in the lungs the efficiency of CO_2 elimination is impaired and carbon dioxide retention results, accompanied by a lowering of the arterial oxygen saturation. When obstruction takes place in the bronchial passageway within the chest, expiration is prolonged since the intrathoracic bronchi constrict during expiration, as the volume of the chest is diminished. Since constriction of the bronchioles is enhanced during expiration, the outlet of air from the alveoli is hindered; the alveolar cells are additionally distended by the succeeding inspiration which puts increased pressure on the pulmonary capillaries and at times results in rupture of their walls. In patients with bronchial asthma an increase in pulmonary ventilation, brought on either by exercise or bronchial spasm, may result in a temporary over-distention of the lung alveoli. This functional pulmonary emphysema may disappear when a remission takes place. In some patients, especially in those in whom infection in the bronchi is present, repeated and prolonged bronchial spasm may result in varying degrees of permanent pulmonary emphysema.

The inhalation of helium with oxygen was shown to result in a lowered negative intrapleural pressure during inspiration in dogs in whom tracheal obstruction had been produced.[8] In one patient with severe asthma the inhalation of an 80 per cent helium 20 per cent oxygen mixture was shown to result also in a substantial decrease in the pathologically elevated negative intrapleural pressure during inspiration.[1]

The substitution of helium for nitrogen is of value in obstructive dyspnea since the velocity of movement of a gas through a constricted orifice is inversely proportional to the square root of the density of the gas. This formula, known as effusion, is the same as the law for diffusion of gases. Since a helium-oxygen mixture is one-third the weight of air or oxygen, the pressure required for the movement of an 80 per cent helium 20 per cent oxygen mixture past a point of localized obstruction was considered to be almost one-half that required for pure

oxygen. Thus, when an oxygen regulator was placed on a helium-oxygen cylinder and set at a liter flow of 1.0, it was observed that the volume of gas passing into a spirometer was 1.7 times the volume of gas that came from a cylinder of oxygen. If the constriction was prolonged in a linear direction, the factor of viscosity would then become involved and, since helium has in fact a slightly higher viscosity than nitrogen, no increase in flow would be observed. In patients with asthma the obstruction is generally in the smaller bronchioles and is fortunately not continued to a sufficiently linear degree as to prevent relief from breathing the helium-oxygen mixture. In some patients, the flow of air is probably modified by both the factors of effusion and viscosity. In localized obstruction in the larynx and trachea the pressure required to breathe helium with oxygen is markedly less than that necessary for ventilating the lungs with oxygen or air.

Dean and Visscher[9] have emphasized turbulence in gas movement, in explaining the relief of dyspnea accomplished by helium-oxygen inhalation in experimental tracheal obstruction; analysis of their formulae reveals that the velocity of turbulent flow is also approximately inversely proportional to the square root of the density of the gas used. We have repeatedly pointed out that there is no change in the effort of respiration during quiet breathing when helium is substituted for nitrogen; its use was proposed for the treatment of *obstructive* dyspnea and its effectiveness in this respect has been confirmed by others.[10,11,12,13]

The effect of inhaling 25 per cent oxygen with 75 per cent helium is, therefore, to diminish the physical pressure required to ventilate the lungs in conditions of laryngeal and tracheal obstruction and severe asthma. This decrease in physical effort (and in the negative intrapleural pressure during inspiration) may be accompanied by a progressive relaxation of the constricted bronchial muscle when the procedure is carried out for one to two hours twice a day for a period of five days.

Positive pressure respiration was added to helium-oxygen administration to increase the relief obtained by inhalational therapy of obstructive dyspnea, and to combat edema of the lungs.[6] The physiological basis of this procedure was described as follows: (1) The specific importance of inhaling a gas under increased pressure is to decrease the pathologically elevated negative intrapulmonary pressure which is present during the inspiratory cycle in cases of obstructive dyspnea. (2) Breathing under a pressure of 10 to 13 cm. of water enormously facili-

tated the entrance of a therapeutic gas during inspiration. (3) During expiration the lumen of the smaller bronchioles was less constricted. (4) The increased intrapulmonary pressure decreased the accumulation of blood in the lungs by exercising a retarding effect on the entrance of blood into the right heart. (5) In animal experiments edema of the lungs was produced when an atmosphere was inhaled under a negative pressure of 6 cm. of water for 6 hours. (6) The inhalation of a gas under positive pressure decreased the suction action of negative pressure on the pulmonary capillaries and in that way tended to clear pulmonary edema.

Poulton,[14] utilizing the suggestion and the apparatus of Plesch,[15] reported that positive pressure breathing afforded "some relief in seven cases of paroxysmal dyspnea" and that "out of eleven cases of asthma good results were obtained in three cases." However, pressure was given in these clinical trials for brief periods only. The relief of paroxysmal dyspnea could be ascribed to a lessened entrance of blood into the right heart and therefore in the lungs, which enabled the left ventricle to deal more effectively with a smaller volume of blood. It had been shown by Weiss and Robb[16] that attacks of cardiac asthma were associated with a sudden increase in the volume of blood in the lungs. The physiological events which took place during the inhalation of oxygen under positive pressure were studied in human subjects and the favorable results that followed the use of continuous positive pressure respiration in some cases of acute pulmonary edema have been described, as well as the apparatus and technique of administering pressure breathing.[17,18,19,20]

Treatment of Intractable Asthma

In the treatment of status asthmaticus an oxygen-enriched atmosphere is provided to prevent respiratory or cardiac failure during the period in which bronchial relaxation is attempted. The inhalation of 50 per cent oxygen in a tent or by means of a catheter inserted in the nasopharynx or oropharynx is better than a mask for oxygen therapy, since most patients with asthma cannot tolerate continuous application of a close-fitting mask to the face. If helium-oxygen therapy is available, inhalation of 25 per cent oxygen with the remainder helium for two hours twice a day, preferably in a positive pressure hood, is employed; the patient is replaced in a tent or given oxygen by catheter

after the helium inhalation. If the hood is not available, the helium-oxygen mixture may be inhaled by a mask but precautions should be taken to maintain a sufficiently adequate flow of the helium-oxygen mixture to prevent negative pressure developing within the mask. If the meter mask is used, the inspiratory valve is either removed, or a match is inserted underneath it so that it is continuously open. A flow of 6 to 9 liters of the helium-oxygen mixture is given for periods of three-quarters of an hour and repeated two or three times during the day.

In the treatment of intractable asthma, in the absence of a grave state of the patient known as status asthmaticus, a similar program of inhalational therapy may be used. In the absence of anoxia the continuous employment of oxygen-enriched atmospheres is not necessary. Since the introduction of intravenous aminophyllin the necessity for keeping patients with status asthmaticus *continuously* in a helium-oxygen atmosphere under positive pressure is no longer present. In a few instances, however, this technique of treatment may be required.

When inhalations of helium-oxygen mixtures are used to produce local bronchial relaxation, the indication is *not* to relieve paroxysms of severe asthma; these may be too severe to be relieved by inhaling helium with oxygen. During the state of slight, moderate, or marked wheezing respiration characteristic of many patients with intractable asthma, the inhalation of helium-oxygen mixtures is of special usefulness. In most patients who are treated efficiently both subjective and objective relief will be apparent as the result of inhaling a mixture of 20 to 25 per cent oxygen and 75 to 80 per cent helium. This relief is more marked when positive pressure hoods are used but is also apparent in mask treatment. The effect of one inhalation is generally to provide only temporary alleviation of symptoms but repeated inhalations of this gas mixture over a period of five days appear to result in a cumulative effect and, therefore, may be used as part of a program of repeated bronchial relaxation. In addition to the local relaxation of the bronchi which this lighter-than-air gas mixture may promote, the negative intrapulmonary pressure during the inspiratory cycle is decreased, so that the mucous membrane of the bronchioles is exposed to a decreased suction effect. In addition, there is better ventilation of the alveoli through constricted orifices.

In recent years we have employed *repeated* injections of aminophyllin in a manner similar to the use of repeated inhalations of helium

with oxygen, at times without inhalational therapy and at other times in conjunction with it. The introduction of intravenous administration of aminophyllin constitutes a landmark in the treatment of intractable asthma.[21, 22] It must be pointed out at the outset, however, that one or two injections of this drug may not result in a satisfactory remission in the symptoms of severe bronchial asthma. In many cases intravenous injection of aminophyllin twice a day for a period of a week and once a day for a period of several weeks to several months might be necessary to break a state of persisting bronchial spasm. Since this would represent an extensive use of intravenous medication, it was fortunately discovered that aminophyllin may be given rectally in watery solution with a beneficial effect almost as great as that obtained from the intravenous route and with the advantages of the absence of circulatory reactions and the obvious usefulness of a method that can be employed by the patient at home.[23]

The technique of administration is important; aminophyllin powders of 0.5, 0.6 or 0.7 Gm. are dissolved in 20 cc. of tap water and instilled into the rectum by a rubber catheter attached to a 20 cc. glass syringe. If a well lubricated No. 10 French catheter is employed the rectal method of injecting aminophyllin is capable of being used by the patient without irritation night and morning for the first week, and for a period of several weeks or several months thereafter, if necessary. Aminophyllin by mouth and by suppository may be helpful in controlling mild or moderate asthma but absorption is too slow to accomplish bronchial relaxation in instances of severe bronchial spasm. Repeated intramuscular injections are impractical because they produce considerable soreness in the gluteal region. The method of rectal instillation is convenient since the patient may have a number of powders made up and quickly provide for himself this type of treatment, with relief of severe asthma, without making it necessary to call a physician to administer an intravenous dose of the drug. In cases that respond favorably to rectal instillation of aminophyllin and the other procedures to be described, a decrease in the severity and incidence of attacks of asthma sets in within a period of five days. A remission may be produced in some cases which lasts from several months to, at times, several years.

The administration of potassium iodide in a dose of 1 cc. of the saturated solution morning and night is considered helpful, not only to

produce a free flow of mucus and to prevent crusting but also because iodides appear to decrease the tendency to asthma. It must be borne in mind that excessive use of iodides may cause a bronchorrhea and thus result in the production of more mucus than the patient will be able to expectorate. In these cases iodides should be stopped for a period of time or given in small doses such as 0.3 or 0.5 cc. daily.

Although morphine may produce respiratory depression if given in excessive dosages, this drug is of great value in many cases, especially when the morphine substitute, dilaudid, is employed. The administration of dilaudid is generally given by mouth, 1/20 gr. to adults, although smaller doses by hypodermic, gr. 1/32 to 1/64, may be given for the first 2 to 5 days. Since this drug may result in addiction, it should be stopped at the end of five days. No instance of respiratory failure or other harmful effect of dilaudid has been observed in over 100 patients in whom it has been used repeatedly during the first 5 days of treatment. The effect of both central nervous system relaxation and bronchial relaxation may be observed in the majority of patients with intractable asthma following its judicious administration. Recently, we have employed demerol in order to accomplish a similar result without the potential hazard of addiction; it is evident that this drug is also of unquestionable value in reducing psychic tension and in promoting bronchial relaxation, given either by mouth or by injection in 100 mg. doses. The injection of sodium luminal is apt to result in better sedation than administration of barbiturate drugs, such as sodium amytal, seconal or nembutal, which sometimes result in irrationality and excitability. A dosage of 0.1 to 0.2 Gm. may be given by hypodermic once or twice a day.

Another procedure that may be of marked value in the program of bronchial relaxation is the inhalation of 1 per cent neosynephrin, carried out by passing oxygen from a high pressure cylinder at a flow of 5 liters per minute through a nebulizer.[23] At two to three hour intervals, 0.5 cc. of 1 per cent neosynephrin is inserted in the nebulizer, and the wide end held within the mouth so that the patient continuously inhales the nebulin of neosynephrin produced by the stream of oxygen. Although this drug is not a good bronchodilator, it exercises a vasoconstricting effect on the mucous membrane and often produces a more patent respiratory passageway, with considerable increase in the vital capacity. The patient with asthma or pulmonary emphysema does not

appear to become refractory to this drug. This procedure of intermittent inhalation of neosynephrin is generally continued for five days. If bronchial infection is present, it may be followed by nebulization of sulfadiazine in 2½ per cent ethanolamine (Pickrell) solution, in dosages of 1.5 cc., repeated in two to three hours.

Epinephrine, 1 to 100, may also be given by this continuous method of nebulization in dosages of 0.2 to 0.5 cc. The hand bulb method of nebulizing epinephrine[24] will generally be effective in relieving asthma after the patient has obtained a degree of bronchial relaxation. During the first 5 days of treatment, epinephrine may be given either by injection or by nebulization to modify the severity of bronchial spasm but since patients with intractable asthma characteristically become refractory to epinephrine in all forms, it is better to postpone use of this drug until the aim of treatment has been accomplished. Repeated injection of adrenalin does not result in cumulative bronchial relaxation, which appears to set in more promptly when epinephrine is dispensed with. Following a favorable outcome of the program described, inhalation of the nebulin of 1 to 100 epinephrine is more satisfactory than hypodermic administration in abolishing attacks of mild or moderate asthma.

In patients with severe inspiratory dyspnea, oxygen-enriched atmospheres, or helium-oxygen mixtures, may be given under continuous positive pressure in a hood designed for this purpose as well as for the treatment of pulmonary edema.[18] The principles and techniques of various types of inhalational therapy have been recently described.[25]

In patients in whom considerable asthma persists after a week of administration of aminophyllin, iodides, dilaudid or demerol, neosynephrin, sodium luminal, either with or without oxygen or helium-oxygen therapy, additional measures should be tried. The rectal injection of ether in doses of 60 to 90 cc. mixed with equal parts of olive oil is at times followed by bronchial relaxation.[26] This may be repeated two or three times at intervals of two days if necessary. In some cases of persisting bronchial spasm, the use of typhoid vaccine to create a slight fever may be helpful. This may be given by intramuscular injection, 1 cc. of the triple typhoid vaccine. A higher fever is more effective and may be produced with a small dose of vaccine when given intravenously. The intravenous injection of typhoid vaccine is more safely administered if 0.2 cc. of the vaccine is added to 1,000 cc. of

normal saline and a slow drip infusion is carried out.[27] When the patient develops a chill the administration of the vaccine in saline may be stopped. If a temperature of 102 to 104°F. has been produced, the severity of the symptoms of asthma may be notably lessened thereafter. However, more than one injection of typhoid vaccine may be required to terminate a state of intractable asthma in some patients.

Although repeated bronchial relaxation is followed by a remission in the symptoms of the disease in the majority of patients with intractable asthma, there are still a good many in whom the relief obtined is unfortunately either temporary or slight. In these patients, continued use of aminophyllin may be necessary either by mouth in dosages of 0.2 Gm. two or three times daily, or rectally, 0.6 Gm. once or twice a day for a long period. In most patients the administration of epinephrine by means of a nebulizer has been found to be more satisfactory than by hypodermic injection for palliative relief. If an *adequate* dosage of aminophyllin is taken, attacks of moderate asthma can generally be controlled by inhaling the nebulin of a 1 per cent epinephrine solution. The inhalation of a nebulized solution is more practical for patients than hypodermic injection and the small dosage results in less systemic effect than parenteral administration.

Summary

Studies of the pathological physiology of obstructive dyspnea indicate that the elevated negative intrapulmonary pressure during the inspiratory cycle exercises a harmful influence on respiratory function. Lowering of this negative pressure by appropriate inhalational and drug therapy is of value in preventing pathological changes in the lungs and intrathoracic bronchi.

Physiologically directed therapy in status asthmaticus may include the inhalation of helium-oxygen mixtures to provide a less effortful type of breathing, or oxygen-enriched air to prevent the effects of anoxia on the cardiac and respiratory systems.

In many patients with intractable bronchial asthma, a program of repeated bronchial relaxation may be pursued without necessarily employing inhalational therapy. The principle of treatment consists of the use of measures which promote relaxation of the constricted bronchial muscle. These include administration of aminophyllin by intravenous or, more conveniently, by rectal instillation of an aqueous

solution, potassium iodide, dilaudid or demerol, neosynephrin by nebulization, and sedation, preferably with sodium luminal. Intermittent inhalation of helium-oxygen mixtures may be added to this regimen since it is helpful during the first 5 days in promoting local bronchial relaxation.

In cases in which the program of bronchial relaxation results in only temporary alleviation of symptoms, a continuation of some of the procedures used is indicated. Administration of aminophyllin in adequate dosages by mouth or by rectal instillation may be required for a prolonged period to prevent recurrence of severe asthma. In these cases, other measures may be tried, such as anesthetic doses of colonic ether and the production of fever with typhoid vaccine.

In the majority of cases of intractable asthma, a more satisfactory remission of the symptoms of the disease may be obtained by the concentrated employment of procedures which produce in one way or another cumulative relaxation of constricted bronchial muscles than by simple palliative therapy.

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